



***Pregnancy, Birth, and Infant Health
Outcomes from the National Smallpox
Health Vaccine in Pregnancy
Registry, 2003–2006***

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Pregnancy, Birth, and Infant Health Outcomes from the National Smallpox Vaccine in Pregnancy Registry, 2003–2006

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When the United States implemented civilian and military smallpox vaccination programs in 2003, the National Smallpox Vaccine in Pregnancy Registry was established to better evaluate outcomes after the inadvertent vaccination of pregnant women. Women were referred to the registry by vaccine administrators, health care providers, or state health departments or through self-referral. Registry professionals actively follow up with all enrolled women and collect data on pregnancy, birth, and infant health outcomes. As of September 2006, pregnancy outcome data were available from 376 women. Most (77%) were vaccinated near the time of conception, before results of a standard pregnancy test would have been positive. To date, outcome evaluations have not revealed higher-than-expected rates of pregnancy loss (11.9%), preterm birth (10.7%), or birth defects (2.8%), compared with those in healthy referent populations. No cases of fetal vaccinia have been identified. The Smallpox Vaccine in Pregnancy Registry continues to actively enroll women and follow infant and early-childhood health outcomes.

In response to concerns about potential biological weapons use worldwide, the United States initiated a national smallpox vaccination program in early 2003 [1]. The vaccine approved for this effort was first used in 1931, and current stocks were produced as Dryvax by Wyeth Laboratories in the late 1970s and early 1980s [2]. Because the vaccine had been administered to billions of individuals over nearly half a century, short-term adverse health effects on vaccine recipients are fairly well documented [2–4]. Historically, much less is described about exposure to smallpox vaccine in pregnancy and the potential effects on a developing fetus.

As a live virus product, smallpox vaccine can cause fetal vaccinia, a rare but serious complication of ex-

posure during pregnancy that often results in fetal or neonatal death [5, 6]. Fetal vaccinia is postulated to occur following maternal viremia and is manifested by skin lesions and internal organ involvement [5, 7]. On the basis of historical data, it is estimated that the risk of fetal vaccinia occurring after smallpox vaccination in pregnancy ranges from 1/10,000 to 1/100,000 [6, 8–12]. Approximately 50 cases of fetal vaccinia have been reported in the world, and 3 have been reported in the United States [4, 5, 7, 12].

In the absence of clinically apparent fetal vaccinia, the risk of pregnancy loss after smallpox vaccination has not been established. Although some large reviews are reassuring that no increased risk exists [8, 12], other reports have cited concern that smallpox vaccination may be associated with spontaneous pregnancy loss [13–17]. Likewise, the risks of preterm delivery, low birth weight, and other birth problems after exposure to smallpox vaccine in pregnancy have not been defined.

Potential adverse effects on infant health also are a concern after maternal exposure. Smallpox vaccination in pregnancy has been associated with club foot mal-

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formations in one report [18]; other reviews have refuted such an association [12]. Given that the cause of most congenital anomalies is unknown and that some have argued that live virus vaccines given during pregnancy might cause birth defects [19–22], more information is needed to understand the risk of infant health problems after maternal smallpox vaccination.

Because of the risk of fetal vaccinia, smallpox vaccine is generally contraindicated during pregnancy. Nonetheless, it was anticipated that vaccinating large numbers of young adults in the national smallpox vaccine program that started in 2003, even with rigorous pregnancy screening, would result in some inadvertent vaccine exposures to pregnant women [23–25]. Accordingly, the National Smallpox Vaccine in Pregnancy Registry was established to identify exposed women and to obtain information on pregnancy, birth, and infant health outcomes. We report the findings from the first 3.5 years of the registry.

METHODS

The National Smallpox Vaccine in Pregnancy Registry was established in concert with the national smallpox vaccine program in early 2003. The registry was developed as a collaborative effort between the US Department of Defense (DoD) and the Centers for Disease Control and Prevention (CDC) and was modeled after prior registries for inadvertent exposure to vaccines or medications in pregnancy [26]. The establishment of the registry was announced in CDC publications and on DoD Web sites [27–29].

Women were enrolled in the registry if they received smallpox vaccine during pregnancy or if they became pregnant within 28 days of vaccination [28]. Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period of the cycle in which a woman conceives; dating of EGA is approximated by ultrasound examination when the timing of the ovulatory cycle is uncertain. We used clinical reports of EGA for establishing dates of all pregnancies in the registry. The registry was also designed to include cases of secondary exposure of pregnant women by, for example, close contact with partners who were recently vaccinated.

Women were referred to the registry by vaccine administrators, obstetric providers, other health care providers, state health departments, DoD Vaccine Healthcare Centers, the Military Vaccine Agency, the CDC Clinical Information Line, or the US Food and Drug Administration; through the Vaccine Adverse Event Reporting System [30]; or through self-referral. Registry professionals actively sought cases by communicating with vaccination and obstetric clinics and shared a standard form for case reporting. The data-collection form included details about vaccination and smallpox vaccine “take,” as well as details about pregnancy diagnosis. Consent was requested to follow up with registry participants and their health care pro-

viders during and after pregnancy, primarily through confidential telephone contact by registry professionals.

Information sheets were provided to enrollees and their health care providers to describe the known and unknown risks associated with smallpox vaccine in pregnancy and to answer frequently asked questions, such as those related to the use of vaccinia immune globulin [31]. The information sheet also specified that, in the event of pregnancy loss or other adverse outcomes, registry professionals would coordinate laboratory testing of fetal or infant specimens (e.g., skin lesions) for vaccinia, if desired. This included viral culture and PCR testing by Laboratory Response Network facilities and/or the CDC Poxvirus Laboratory [32].

Expected rates for outcomes examined were determined by literature review and by identifying relevant key publications from subject matter experts. We calculated 95% CIs for dichotomous outcomes on the basis of normal approximation of the binomial distribution. For outcome cell counts <5, exact CIs were calculated [33].

This research, performed under Naval Health Research Center Institutional Review Board–approved protocol 2003.0018, under work unit 60504, has been conducted in compliance with all applicable federal regulations governing the protection of human subjects in research.

RESULTS

As of September 2006, pregnancy outcome data were available for 376 women enrolled in the Smallpox Vaccine in Pregnancy Registry. Women who had not yet reached the 20th week of pregnancy at the time of this report ($n = 7$), enrolled women who had a secondary exposure from the husband’s vaccination only ($n = 4$), and enrolled women who were lost to follow-up ($n = 3$) are excluded from this report.

Table 1 shows the characteristics of the 376 women for whom pregnancy outcome data were available. Consistent with the

Table 1. Characteristics of 376 women inadvertently vaccinated against smallpox in pregnancy.

Characteristic	Value
Age at vaccination, mean years (range)	23.2 (17–41)
Vaccinated as part of military service	365 (97.1)
Vaccinated while deployed outside of United States	91 (24.2)
No history of prior smallpox vaccination	354 (94.1)
No history of previous pregnancies (primigravid)	199 (52.9)
Vaccinated before 4 weeks EGA	289 (76.9)
Received other vaccinations in this pregnancy ^a	260 (69.1)

NOTE. Data are no. (%) of women unless otherwise indicated. EGA, estimated gestational age.

^a Receipt of other vaccinations in pregnancy is based on the registry standard of exposure within 28 days before start of EGA or any time from conception to the end of pregnancy. If preconception exposures are excluded, 162 cases (43.1%) had other vaccinations in pregnancy.

US experience since 2002, most women (97.1%) received smallpox vaccine as part of their military service, and the remaining 11 women were vaccinated as civilian health care workers. Ninety-four percent of women had no history of prior smallpox vaccination. Prior smallpox vaccination was confirmed by review of personal histories and by vaccination records showing receipt of the 15-jab inoculation that is consistent with revaccination. Among military women, 72% served in the Army, 17% served in the Air Force, and 10% served in the Navy or Marine Corps. Some women ($n = 91$) were vaccinated while on military duty outside of the United States, and many ($n = 260$) received other vaccinations in conjunction with the smallpox vaccine. Other vaccinations reported by registry participants included anthrax ($n = 228$), hepatitis A or B ($n = 50$), typhoid ($n = 46$), influenza ($n = 34$), yellow fever ($n = 18$), meningococcal ($n = 14$), tetanus or tetanus-diphtheria ($n = 8$), measles-mumps-rubella ($n = 7$), polio ($n = 2$), and pneumococcal ($n = 1$) vaccines.

Most women (77%) in the registry were vaccinated before 4 weeks EGA, the time after which results of a standard pregnancy test should be positive. Figure 1 shows that most women were vaccinated very near the estimated time of conception.

Pregnancy outcomes are summarized in table 2. Among 376 pregnant women, 5 had twin pregnancies, for a total of 381 fetal outcomes. Five ectopic pregnancies represented 1.2% of all pregnancies reported to the registry. The 18 elective pregnancy terminations represented 4.7% of all fetal outcomes. No registry participants cited their inadvertent smallpox vaccination as a reason for pursuing elective termination of pregnancy. Population references for ectopic pregnancy and elective termination are also shown in table 2 [34, 35].

Forty-two spontaneous fetal losses were identified in the registry. Although these represent 11.0% of all fetal outcomes, the

spontaneous loss rate may be more appropriately calculated on the basis of the number of intrauterine pregnancies that were not electively terminated, yielding a loss rate of 11.9%. Population references for expected rates of pregnancy loss are also shown in table 2 [36–41]. Figure 1 illustrates pregnancy outcomes, including losses, by timing of maternal exposure to smallpox vaccine. The largest percentage of fetal losses (20.6%) occurred among women vaccinated between 4 and 7 weeks EGA. Fetal tissue was available from 5 losses for vaccinia testing; results of all such testing were negative for vaccinia virus.

Birth and infant health outcomes are summarized in table 2. The percentage of preterm births (10.7%) among registry births, the average birth weight of singleton registry infants (3320 g), and the percentage of infants with low birth weight (9.1%) may be compared with national data shown in table 2 [42]. Nearly half (47.9%) of all infants born to women in the Smallpox Vaccine in Pregnancy Registry were male; this may be compared with the current US national proportion of male births [43].

Finally, important health outcomes are shown in table 2 for all live-born infants evaluated through the end of infancy or 12 months of age. Two infants in the registry died of sudden infant death syndrome (SIDS), at 7 weeks and 9 weeks of age, respectively. The expected rate of SIDS is 4.7 per 10,000 live births [44, 45]. Both infants who died of SIDS from the registry had postmortem testing for vaccinia virus, and all test results were negative.

Seven infants (2.8%) had diagnoses of major birth defects, as defined by the National Birth Defects Prevention Network [46]. Their diagnoses included ventricular septal defects (2 cases), atrial septal defect (1 case), pulmonary valve stenosis (1 case), isolated gastroschisis (1 case), isolated omphalocele (1 case), and omphalocele with Beckwith-Weidemann syndrome

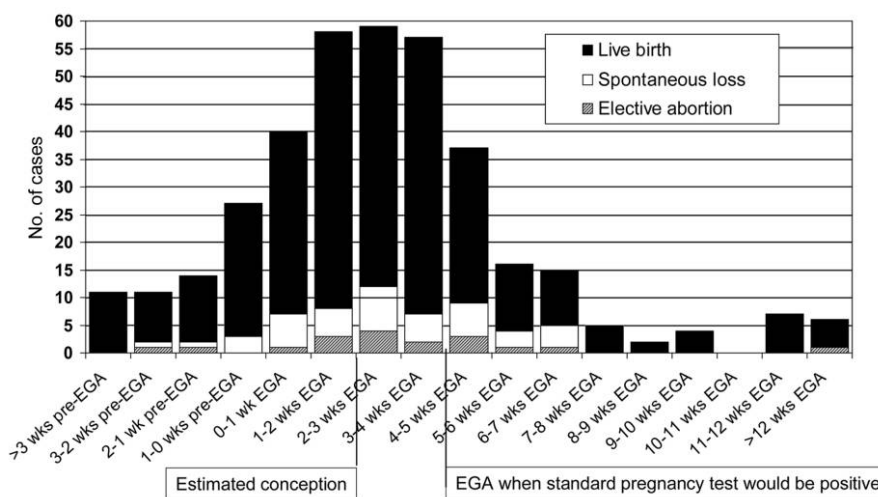


Figure 1. Pregnancy outcomes according to estimated gestational age (EGA) at the time of maternal smallpox vaccination. wk, week.

Table 2. Pregnancy, birth, and infant health outcomes among those enrolled in the Smallpox Vaccine in Pregnancy Registry, 2003–2006.

Outcome	Value	Percentage (95% CI)	Reference value(s) (source)
Fetal outcomes (<i>n</i> = 381)			
Ectopic pregnancy	5	1.3 (0.2–2.4)	1–2 [34]
Elective abortion	18	5.8 ^a (3.2–8.3)	24.6 [35]
Spontaneous abortion (loss before 20 weeks EGA)	37	9.7 (6.7–12.7)	9–30 [36–40]
Stillbirth (loss after 20 weeks EGA)	5	1.0 ^b (0.0–2.1)	0.3–0.7 [41]
Fetal vaccinia	0	0.0 (0.0–0.9)	0.01–0.001 [4]
Live birth outcomes ^c (<i>n</i> = 309)			
Preterm birth (before 37 weeks EGA)	33	10.7 (7.3–14.1)	12.3 [42]
Low birth weight (<2500 g)	28	9.1 (5.9–12.3)	7.9 [42]
Mean birth weight, g	3320	...	3325 [42]
Male sex of infant	148	47.9 (42.3–53.6)	52 [43]
Infant health outcomes ^d (<i>n</i> = 249)			
Sudden infant death syndrome	2	0.8 (0.0–2.9)	0.05 [44, 45]
Major birth defects ^e	7	2.8 (0.8–4.8)	3–5 [46]

NOTE. Data are no. of cases, unless otherwise indicated. EGA, estimated gestational age.

^a Standard reporting for this metric is the ratio of elective abortions to 100 live births.

^b Standard reporting for this metric is the proportion of singleton stillbirths among all singleton live births plus stillbirths. One set of stillborn twins and all live-born twins were excluded from this calculation.

^c Note that 7 cases in late pregnancy at the time of this report had no birth outcomes available.

^d Infant health outcomes reported for those with follow-up through end of infancy or 12 months of age.

^e A major birth defect is one that affects survival, requires substantial medical care, results in marked physical or psychological handicaps, or interferes with a baby's prospect for a productive and fulfilling life [46].

(1 case). The observed prevalence of birth defects (2.8%) may be compared with national data, also shown in table 2 [46].

At all follow-up contacts, registry participants were asked about other indicators of infant health, including skin lesions. Many infants (44%) had some indication of skin findings at birth or in early infancy; most were considered to be birthmarks or benign rashes, and none had diagnoses of fetal vaccinia.

DISCUSSION

The Smallpox Vaccine in Pregnancy Registry was successfully established in 2003 to evaluate inadvertent vaccine exposures in pregnancy. The effort has been important in providing a better understanding of potential adverse effects of smallpox vaccination in a vulnerable population. With nearly 400 women enrolled, there have been no cases of fetal vaccinia identified. Other adverse outcomes of pregnancy, birth, and infant development have been observed at rates consistent with those expected in the United States and previously described [34–46]. Although active vaccination of civilians for public health preparedness is not ongoing in the United States, as smallpox vaccine continues to be used in the military and vaccine remains available for postevent response [47], these registry data will be important in directing public health policy decisions.

Although the modest numbers of enrollees in the Smallpox Vaccine in Pregnancy Registry do not allow for definitive conclusions about many important outcomes, such as fetal vac-

cinia, the results are valuable in a number of ways. As evaluated in early 2003, established smallpox vaccine screening and education practices appeared to have prevented many exposures in pregnancy [28]. The rate of inadvertent exposure during pregnancy among women of reproductive age vaccinated during the first stage of the civilian and DoD programs was ~1 per 1000 women, substantially lower than the ~8 per 1000 women and 12 per 1000 women estimated to be inadvertently exposed to smallpox vaccine in the civilian health care worker population and in the general population, respectively, in the absence of screening and education [28]. Therefore, most women who were vaccinated were in the very early stages of pregnancy, when pregnancy is typically not yet recognized.

The registry may be most valuable with regard to conclusions about pregnancy losses. The most frequently expected adverse outcome in any cohort of pregnancies is spontaneous pregnancy loss, and, as such, pregnancy loss may be one of the most important indicators of hazardous exposure in the spectrum of adverse reproductive health outcomes [48]. Without active registry follow-up, most pregnancy-loss data would not have been captured, and it is unlikely that testing for vaccinia would have been performed on loss cases. The relatively low rate of observed pregnancy losses may, therefore, be considered a reassuring finding within the registry.

It remains important to consider losses, and all adverse outcomes, in relation to the timing of exposure in pregnancy. Given

that fetal development is so dynamic, there are some periods of pregnancy that represent more vulnerable times for certain adverse outcomes. For this reason, the timing of maternal smallpox vaccination was explored in relation to pregnancy losses. There were no statistically significant associations between timing of exposure and the pregnancy outcomes examined. However, the small number of cases in which vaccination occurred later than 4 weeks EGA limited such interpretations. Follow-up of the registry will continue to address the issue of exposure timing.

Birth outcomes are other important metrics for evaluating potential hazardous exposures in pregnancy. In the Smallpox Vaccine in Pregnancy Registry, the expected rates of all outcomes examined fell within the 95% CIs of observed rates, including measures of low birth weight and preterm birth. The proportion of registry infants who were male was within the expected range, and this may also be considered a reassuring finding, because a reduced proportion of male infant births may reflect occult hazardous exposures in a population [49].

Finally, adverse infant health outcomes are of unique importance, because they represent some of the most visible and costly negative reproductive health outcomes. The absence of cases of fetal vaccinia in the Smallpox Vaccine in Pregnancy Registry to date is not unexpected, given the low estimated risk for fetal vaccinia. Although 7 infants with birth defects were identified, the rates and distribution of these birth defects were not outside of expected ranges [46]. The 2 cases of SIDS, however, were unexpected occurrences within this small cohort of infants. Given the uncertain etiology of most SIDS cases and the uncertain effects of maternal smallpox vaccination, these cases may illustrate the important value of the registry's coordination of vaccinia testing in helping to evaluate an unusual association.

The following limitations should be considered when interpreting these data. First, the majority of women were vaccinated early in pregnancy, before 4 weeks EGA. This period of pregnancy includes weeks before the embryo implants; thus, transmission of vaccinia virus from mother to embryo would be unlikely. Small numbers of cases limited our ability to examine possible effects of smallpox vaccine exposure later in pregnancy, when maternal viremia may be more likely to result in transmission across the placenta and when outcomes may also differ. We could not determine the capture rate of all eligible cases for the registry. The rate of capture of military cases, however, is being evaluated through a separate effort, outside of the scope of this report. There are limitations to relying on prior publications and subject matter experts when defining "expected rates" of pregnancy, birth, and infant health outcomes. We could not assess the extent to which our study population differed from those of other studies, and rates of outcomes

such as spontaneous abortion can vary greatly, depending on the method of ascertainment [36].

The Smallpox Vaccine in Pregnancy Registry continues to actively enroll and follow up with women who have been vaccinated in pregnancy, as well as to follow their children's health outcomes. Most vaccinations are now occurring among military personnel, although small numbers of civilians may continue to receive smallpox vaccine for public health preparedness. The first infants born to registry participants reached 3 years of age in 2006. Registry professionals have collected health and developmental information about these children at least annually so that, in the future, even more challenging questions about the long-term effects of smallpox vaccination in pregnancy might be explored.

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14. ABSTRACT (maximum 200 words)
Background: Little information is available to describe the risks of smallpox vaccine administered in pregnancy, with the exception of known, rare cases of fetal vaccinia. When the United States implemented a smallpox vaccination program in 2003, the Smallpox Vaccine in Pregnancy Registry was established to better evaluate outcomes after the inadvertent vaccination of women in pregnancy.
Methods: The Registry developed a modified Vaccine Adverse Event Reporting System report to collect information from pregnant women after smallpox vaccination. Military healthcare providers were engaged to identify cases, since most smallpox vaccines were administered to military service members. Registry professionals actively follow all enrolled women through and after pregnancy.
Results: As of September 2006, pregnancy outcome data were available from 376 women followed by the Registry. Most (77%) were vaccinated near the time of conception, before a standard pregnancy test would have been positive. Evaluations of outcomes to date have not revealed higher-than-expected rates of pregnancy loss (11.9%), preterm birth (10.7%), or birth defects (2.8%), when compared to healthy referent populations. No cases of fetal vaccinia have been identified.
Conclusions: Close follow-up of women inadvertently vaccinated against smallpox during pregnancy, to date, has not revealed pregnancy, birth, or infant health problems attributable to smallpox vaccine exposure. The Smallpox Vaccine in Pregnancy Registry continues to actively enroll and follow women and infant and early childhood health outcomes.

15. SUBJECT TERMS
smallpox vaccine, vaccinia, pregnancy, reproductive health

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